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EXAMINER	
OGUNBIYI, OLUWATOSIN A	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/529,654	VEDRINE ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 9/16/09 has been entered into the record. Claims 1-22 are pending. Claims 1-17 and 21-22 are under examination. Claims 18-20 are withdrawn.

Election/Restrictions

This application contains claims 18-20 drawn to an invention nonelected with traverse in the response filed 9/15/08 A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

The objection to the specification is withdrawn in view of the amended abstract.

Rejections Withdrawn

The rejection of claims 1-17 under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendment to the claims.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1, 4, 5, 6, 11, 14, 15 and 17 under 35 U.S.C. 103(a) as being unpatentable over Berg et al. WO 89/04372, 18th May 1989 (cited in IDS) in view of Pyle et al WO 95/31481 23 November 1995 (cited in IDS) is maintained.

The claims are drawn to a method for detecting and counting the microorganisms in a sample comprising the steps of:

a) selectively enriching the microorganism sought in the sample,

b) inducing or activating at least one enzymatic activity of the microorganism,

c) immunomagnetically concentrating the

microorganism,

d) fluorescently labeling the microorganism by adding to the sample containing the microorganism at least one substrate comprising one part specific to the enzymatic activity to be indicated and one fluorogenic label, wherein the transformation of the substrate takes place inside the microorganism and that the fluorescent product resulting from the fluorogenic label is retained in the microorganism, and

e) detecting and counting the fluorescence labeled
microorganisms by fluorescence microscopy.

Berg et al teaches a method of assaying a dilute concentration of living pathogenic microorganisms in a sample of product for human consumption, comprising contacting a sample comprising microorganisms e.g. bacteria with a nutrient medium capable of supporting the metabolism and reproduction of the microorganisms (selectively enriching the microorganisms sought in the sample), inducing the production of an enzyme in said microorganism by contacting said microorganism with an agent such as lactose that is capable of inducing the production of an enzyme (specific to the microorganism sought) in said microorganism (inducing or activating at least one enzymatic activity), then contacting by adding to the media containing the enzymatically induced microorganism a substrate which reacts with the enzyme (one part specific to the enzymatic activity) to release the fluorescent portion thereof (fluorogenic label part), and adding a permeability agent which increases the permeability of the microorganisms to the enzyme or fluorogenic substrate or both and incubating the cells to permit contacting of the enzyme (whether inside or outside the microorganism) with the fluorogenic substrate and the release of the fluorescent portion of the fluorogenic substrate. Berg et al teaches a step wherein the amount of fluorescence emitted is calculated and the concentration of microorganisms is determined by counting the number of fluorescent microclonies (fluorescence microscopy). See p. 6 -7, p. 9 lines 14-15 and p. 21-22 claim 1.

As to claim 5, Berg et al teaches that selectively enriching the microorganism and inducing or activating the enzymatic activity can be carried out simultaneously since Berg et al teaches that the microorganisms are initially contacted with an actuating medium that comprises 1) the nutrient media or selectively enriching the microorganism and 2) the production agent e.g. lactose. See p. 6 lines 5-15.

As to claim 11, Berg et al teaches that the fluorescent labeling of the microorganism is carried out by adding to said actuating media the fluorogenic substrate which comprises a substrate part specific to said enzymatic activity and a fluorescent label part (e.g. fluorogenic substrates: 4-methylumbeliferone-heptanoate p. 7 lines 19-24, or 4-methylumbeliferone-beta-D-galactoside, p. 14 line 20-25, wherein cleavage by induced enzymes reveals fluorescent 4-methylumbeliferone). See p. 6 lines 5-15.

As to claim 15 and 17, Berg et al teaches that the sample can be filtered before commencing on the steps of detecting and counting the microorganism e.g. see p. 12 0.2 um to 0.8um pore size, p. 14 example 1 lines 11-14 using filter pore size 0. 045 um, p. 19 lines 8-10.

Berg et al does not teach immunomagnetically concentrating the enzymatically activated microorganism after the fluorescent labeling of the microorganism, and does not teach immunomagnetically concentrating the microorganisms before inducing enzymatic activity.

Pyle et al teaches a method for detection and enumeration of viable microorganisms in a sample. Pyle et al also relies on a metabolic indicator and uses immunomagnetic separation/concentration using antibodies which specifically binds to a target bacteria to concentrate the bacteria before addition of a metabolic indicator and before detection of fluorescence. See p. 38 lines 1-29. Pyle et al teaches that immunomagnetic separation is a widely used method for facilitation concentration and separation from samples (see p. 38 lines 30 to p. 40) and that immunomagnetic capture not only permits cell concentration but also the selection of a specific antigenic cell type. See p. 41 lines 7-19.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to have immunomagnetically concentrated the enzymatically induced microorganisms of Berg et al before addition of the fluorogenic substrate in order to concentrate a specific antigenic cell type in the sample prior to the fluorescent labeling and counting as taught by Pyle et al (p. 38 lines 30 to p. 40) who teaches that immunomagnetic capture non only permits cell concentration but also the selection of a specific antigenic cell type), thus resulting in the instant invention with a reasonable expectation of success. As to claim 6, it would have been prima facie obvious in said method of Berg et al to immunomagnetically concentrate the microorganisms in the sample before the enriching step or enzyme induction (immunomagnetic concentration before induction or activation of enzymatic activity) or immunomagnetically concentrating the microorganisms after fluorescence labeling, so as to concentrate a specific antigenic cell type in said sample of Berg et al, thus resulting in the instant invention with a reasonable expectation of success. Pyle et al teaches that immunomagnetic capture/concentration not only permits cell concentration but also the selection of a specific antigenic cell type (see p. 41 lines 7-19) and there would have been a reasonable expectation of detecting and counting

microorganisms irrespective of when specific antigenic type of microorganism is concentrated or captured from the sample.

Applicants' arguments:

Applicants argue that Berg does not disclose a strictly intracellular labeling for purposes of enabling a numeration or counting of the microorganisms, nor a step of numeration or counting of the microorganism. These distinctions are important for the following reasons: of 10 (see page 18, lines 9 to 14 of the specification as filed);

- the strictly intracellular labeling permits a direct and quick numeration or counting of microorganisms. Berg uses a counting method that requires many steps. Specifically, Berg uses permeability agents which necessitates many measures and then requires a comparison with a standard curve to determine the concentration of microorganisms in the sample; and

- the enumeration or counting of the microorganisms by a technique chosen from the group comprising flow cytometry, filtration cytometry and fluorescence microscopy is fast and reliable.

Thus, the technical effects associated with these differences permits an accelerated microorganism detection, in less than 24 hours for some of them, with the detection being carried out with a better sensitivity and specificity than the one obtained according to the methods described in Berg. The benefits of applicants invention relative to the prior art are described in the specification at page 13.

The Examiner has cited Pyle for its teaching of a method for detection and enumeration of viable microorganisms in a sample, which relies on a metabolic indicator and uses immunomagnetic separation and concentration using antibodies that specifically bind to a target bacteria. According to the Examiner, it would have been *prima facie* obvious to immunomagnetically concentrate the enzymatically induced microorganisms of Berg, in view of the teachings of Pyle.

Applicants argue that Pyle does not remedy the deficiencies of Berg, which does not describe, nor suggest, the important specificity and sensitivity obtained with the claimed method, nor the reduced time needed to carry out this method.

Response:

Applicants' arguments have been carefully considered but are not found persuasive. Although, USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure (In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997)), limitations appearing in the specification but not recited in the claim should not be read into the claim. E-Pass Techs., Inc. v. 3Com Corp. , 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily). Applicants argument that Berg does not disclose strictly intracellular labeling is not commensurate with the scope of the claims because the claims do not disclose " strictly intracellular labeling" of microorganisms. Berg et al gives the option of contacting the enzyme inside or outside of the microorganism with the fluorogenic substrate. Thus, Berg et al teaches intracellular labeling of the microorganisms. The instant method "comprises" and thus does not exclude other counting method steps. Berg et al teaches each of the method steps including transformation of the substrate inside the microorganism and retention of the fluorescent part of the substrate in the microorganism and the counting of fluorescent microorganism by fluorescence microscopy except for immunomagnetic concentration which is rendered obvious by the teachings of Pyle et al as set forth supra.

The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Berg et al. WO 89/04372, 18th May 1989 and Pyle et al WO 95/31481 23 November 1995 as applied to claims 1, 4,5,6, 11, 14, 15 and 17 above, further in view of Sigma catalog 1996 p. 2179-2181 is maintained.

The combination of Berg and Pyle is set forth supra. Said combination does not teach a filtration step before a), b) c), d) and e) using a filter whose porosity size is 20-100 microns.

Sigma catalog teaches filters with various porosity size (retention size) including between 20-25 and 30 microns. See p. 2181.

Since the combination of Berg and Pyle et al teach detection of microorganisms in water comprising sewage effluent or raw domestic sewage (see Berg et al, example 1, p. 1), it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention

was made to filter the water sample containing sewage using a filter with large pore size e.g. 20-25 or 30 microns or larger (see Sigma catalog p. 2181) to remove any particulate matter prior to enriching microorganisms in the sample, thus aiding the detecting and counting process and resulting in the instant invention with a reasonable expectation of success.

Applicants' arguments:

Applicants traverse this rejection for reasons set forth above in connection with the rejection over Berg and Pyle. Applicants agree that filters of various porosity were available at the time of the invention. However, nothing in the cited art directs the skilled artisan to porosity sizes within the claimed ranges. As such, applicants do not agree that the subject matter of claim 16 would have been obvious to the skilled artisan. Withdrawal of this rejection is respectfully requested.

Response:

Applicants' arguments are carefully considered but are not persuasive. Applicants agree that filters of various porosity were available at the time of the invention. The rejection of Berg in view of Pyle et al is maintained as set forth above. In addition, one of skill in the art would have selected the filters of Sigma catalog depending on the sample to be filtered to remove large particles e.g. from samples for human consumption or sewage effluent (e.g. food see claim 1 p. 21, p. 1 and p. 14 of Berg et al). The Sigma catalog teaches the that 20-25 and 30 um filters are good for retention of large particles.

The rejection of claims 8, 9, 10 under 35 U.S.C. 103(a) as being unpatentable over Berg et al. WO 89/04372, 18th May 1989 and Pyle et al WO 95/31481 23 November 1995 as applied to claims 1, 4, 5, 6, 11, 14, 15 and 17 above, further in view of Olsen et al. Plant and Soil 186:75-79, 1996 is maintained.

The combination of Berg and Pyle is set forth supra. Said combination does not teach (claim 8) that the immunomagnetic concentration step comprises a) placing the microorganism sought, present in the sample, in contact with an antibody directed against an antigen specific to

the microorganism, the antibody being conjugated with a magnetic bead, b) separating the bead-antibody-microorganism complexes from the
sample, and c) separating the microorganism from the rest of the complex; does not teach (claim 9) a method according to claim 8, wherein the antibody conjugated
with a magnetic bead is directed against an antibody that is itself directed against an antigen specific to the microorganism sought; does not teach (claim 10) a method according to claim 8 or 9, wherein the magnetic beads have a diameter that is between 1 and 20 um, or between 2 and 8 um.

Olsen et al teaches a method of detecting and counting the number of bacteria in sample using immunomagnetic concentration before detecting and counting of the concentrated cells by fluorescence microscopy. See p. 77 column 1 and column 2 figure 2. The immunomagnetic procedure uses magnetic beads that are 2.8 um in diameter, p. 76 column 2 under immunomagnetic beads, and comprises contacting the bacteria in the sample with an antibody directed against the bacteria, separating the bead antibody bacteria complexes from the medium and separating the microorganism from the rest of the complex by vortexing to detach the beads and separation of the beads via magnetization (see p. 77 column 1 under analytical procedure). Said magnetic bead also comprises a secondary antibody that is directed to the antibody that is directed to the bacteria, which aids in detection of the bacteria.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to carry out the immunomagnetic concentration step of Berg et al and Pyle et al as combined using the known immunomagnetic concentration guideline set forth in Olsen et al which involves contacting the bacteria in the sample with an antibody directed against the bacteria being sought, separating the bead antibody bacteria complexes from the medium and separating the microorganism from the rest of the complex by vortexing to detach the beads and separation of the beads via magnetization procedure and using magnetic bead comprising a secondary antibody that is directed to the antibody that is directed to the bacteria, which aids in detection of the bacteria, (see p. 77 column 1 under analytical), thus arriving at the instant invention with a reasonable success. The combination of Berg et al and Pyle et al teach a method of detecting and counting bacteria in a sample using the combination of immunomagnetic separation and fluorescence microscopy and Olsen et al also teaches a method

of detecting and counting the number of bacteria in sample using immunomagnetic concentration band detecting and counting of the concentrated cells by fluorescence microscopy, it would have been prima facie obvious to adapt the general immunomagnetic concentration protocol set forth in Olsen et al and tailor said protocol for the immunomagnetic concentration step in Berg and Pyle et al as combined as both immunomagnetic concentration techniques are essentially accomplishing the same thing i.e. concentration of a specific antigenic type of bacteria from a sample.

Applicants' arguments:

Applicants respectfully traverse this rejection for reasons set forth above with regard to the teachings of Berg and Pyle. Olsen teaches an immunomagnetic method used for separating bacteria from a sample. However, it does not teach or suggest the other steps recited in independent claim so it does not remedy the deficiencies in Berg and Pyle.

Response:

Applicants' arguments are carefully considered but are not persuasive. The rejection of Berg in view of Pyle et al is maintained for the reasons set forth above.

The rejections of claims 12 and 13 under 35 U.S.C. 103(a) as being unpatentable over Berg et al. WO 89/04372, 18th May 1989 and Pyle et al WO 95/31481 23 November 1995 as applied to claims 1, 4,5,6, 11, 14, 15 and 17 above, further in view of Boyd et al US 5,510,243 Apr. 23 1996 is maintained.

The combination of Berg and Pyle is set forth supra. Said combination does not teach the use of a monosaccharide substrate part specific to the enzymatic activity to be revealed and does not teach that the fluorogenic label is a xanthene.

Boyd et al teaches the method of detecting bacteria *E. coli* and discriminating between said *E. coli* and non-target bacteria using fluorogenic substrates such as fluorescein-di-beta-D-galactopyranoside which has a label part that is a xanthene i.e. fluorescein and a substrate part (di-beta-D-galactopyranoside) comprising a monosaccharide which is specific to Beta-

galactosidase enzyme and Boyd et al teaches the use of galactosidase inducers e.g. IPTG to include in media comprising the *E. coli* to be detected. See column 3 line 14-16, 50 to 667 to column 4 lines 1-6 and 60- 67.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to substitute the fluorogenic substrate (which comprises a substrate part and label part) and the enzymatic inducer of the combination of Berg and Pyle with another fluorogenic substrate and inducer known in the art for detection of bacteria in a sample such as fluorescein-di-beta-D-galactopyranoside which has a label part that is a xanthene i.e. fluorescein and a substrate part (di-beta-D-galactopyranoside) comprising a monosaccharide which is specific to Beta-galactosidase enzyme and the galactosidase inducer e.g. IPTG (see Boyd et al column 3 line 14-16, 50 to 67 to column 4 lines 1-6 and 60- 67), thus resulting in the instant invention with a reasonable expectation of success. It is prima facie obvious to substitute known fluorogenic substrate and inducer systems as they are similarly used for the same thing i.e. detecting bacteria in a sample.

Applicants' arguments:

Applicants respectfully traverse this rejection for the reason set forth above in connection with Berg and Pyle. Boyd fails to remedy the deficiencies in the primary references.

Response:

Applicants' arguments are carefully considered but are not persuasive. The rejection of Berg in view of Pyle et al is maintained for the reasons set forth above.

The rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Berg et al. WO 89/04372, 18th May 1989 and Pyle et al WO 95/31481 23 November 1995 as applied to claims 1, 4, 5, 6, 11, 14, 15 and 17 above, further in view of Kaclikova et al. Journal of Microbiological Methods, Vol. 46 Issue 1 July 2001, p. 63-67 is maintained.

Berg and Pyle et al as combined is set forth supra. The combination does not teach addition of yeast extract to the enrichment medium.

Kaclikova et al teaches a method of detecting *Listeria* in a product for human consumption (cheese) using enrichment media (Fraser broth) and immunomagnetic separation. See p. 63 column 2 lines 1-3 and p. 64. under section 2.4. Half-Fraser broth comprises amongst other things yeast extract 5g/L[1].

Since the combination of Berg and Pyle is drawn to detection and counting of pathogenic microorganisms in a sample of product for human consumption (see abstract of Berg et al), it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to modify the enrichment media of Berg and Pyle as combined by adding nutrients for enriching and detecting other pathogenic microorganisms in products for human consumption such as *Listeria*. Kaclikova et al teaches a method of detecting Listeria in food samples (see title). Said nutrients include those contained in Half-Fraser enrichment broth for detecting of Listeria which comprises yeast extract (see Kaclikova et al p. 63 column 2 lines 1-3 and p. 64. under section 2.4., thus resulting in the instant invention with a reasonable expectation of success.

[1]Technical Bulletin for Fraser Listeria Enrichment Broth Base: for the selective enrichment of Listeria in the 2-step method acc. to D.G.AL. and ISO 11290-1 (1996). EMD Merck KGaA, Damstadt, Germany, 2002.
http://www.emdchemicals.com/analytics/Micro_Manual/TEDISdata/prods/1_10398_0500.html. Retrieved, March 9, 2009.

Applicants' arguments:

Kaclikova teaches a method of detecting *Listeria* in which the pathogens are enriched with a Half-Fraser broth, which is said to contain yeast extract. Applicants respectfully traverse this rejection. First, Kaclikova teaches against the use of using a half-Frasier enrichment broth, stating that this method had significant drawbacks associated with time-consuming cultures (page 63). The point of Kaclikova's work was to develop an improvement over the prior half-Frasier/Frasier methods. In any event, nothing in Kaclikova remedies the deficiencies in the primary references.

Response:

Applicants' arguments are carefully considered but are not persuasive. Kaclikova does not teach against the use of using half-Frasier broth because Kaclikova teaches the use of half-Frasier broth i.e. cheese samples where subjected to immunoseperation and a sample was homogenized in 225 ml of half Frasier broth and incubated for 24h at 30oC. See p. 64 section. 2.4. The "teaching" away portion Applicants rely upon on p. 63 column has to do with standard detection method for L. monocytogenes in food involving a two-stage enrichment in half-Fraser and Fraser broths, plating on agar and identification of colonies by biochemical tests and the Kaclikova et al teaches the drawback of the method which is the time requirement which can be overcome by using immunomagnetic separation. Clearly, Kaclikova proceeds to use the immunoseperation method coupled with enrichment in half-Fraser broth. The improvement stated in Kaclikova et al is the immunoseperation method and not the use of half-Frasier broths in enriching for Listeria.

New Rejections Based on Amendment

Claims 2-3 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berg et al. WO 89/04372, 18th May 1989 (cited in IDS) and Pyle et al WO 95/31481 23 November 1995 (cited in IDS) as applied to claims 1, 4, 5, 6, 11, 14, 15 and 17 above, further in view of Strenkoski et al. (US 5,843,699 Dec. 1 1998) and Heck et al (US 3,704,204) Nov. 28, 1972) and Ray, Bibek (Injured Index and Pathogenic Bacteria. 1989. CRC Press Inc. Boca Raton, Florida. Page 78) and Patel et al. (Journal of Food Protection, 1995 vol. 58, No. 3, p. 244-250)

The combination of Berg et al and Pyle et al is set forth supra. Said combination does not teach enriching the microorganisms in a composition comprising sodium pyruvate, sodium thiosulfate and catalase.

Strenkoski et al teaches that recovering pathogenic microorganisms from a food samples involves a pre-enrichment wherein the food sample is enriched to restore injured bacterial cells to a stable physiological condition. Column 2 lines 53-55. Strenkoski et al also teaches that the pre-enrichment media can comprise a mildly selective inhibitor such as an antibiotic and that the

selection of antibiotic inhibitor depends on the selected target microorganism. See column 6 lines 56-67 and column 7 lines 1-6. Strenkoski et al teaches at least one selective inhibitor or mixtures thereof can be added to the pre-enrichment media and teaches that sodium thiosulfate is a selective inhibitor. Column 7 lines 16-20 and 38-60.

Heck et al teaches sodium thiosulfate as a selective inhibitor at a concentration of about 0.03% -0.07% by weight. See column 2 lines 61-65.

Ray teaches that catalase and pyruvate also increases the count levels of Salmonella in enrichment and teaches that both of these reagents are able to react with or catalyze the decomposition of the toxic substance, hydrogen peroxide. See p. 78.

Patel et al teaches that since injured bacterial cells typically have increased sensitivity to hydrogen peroxide and superoxide radicals, due to decreased catalase and superoxide dismutase activities, the addition of pyruvate and catalase has been recommended to maximize repair and colony formation of injured S. aureus cells. See page 247 column 2 under discussion. Patel et al teaches supplementation of 1% pyruvate or 0.04% catalase to support an increased level of repair of heat injured L. monocytogenes. See page 247 column 2 under discussion. Patel also teaches that at 2.5 mg/mL (2.5 g/L) sodium pyruvate and 400 μg/ml catalase, injured cells under went resuscitation. See abstract. Patel et al also tested other concentrations of catalase and sodium pyruvate in table 1 p. 246. See whole of Patel.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to add to the media of the selective enrichment step of the combination of Berg and Pyle, sodium pyruvate, sodium thiosulfate and catalase because Strenkoski et al teaches that sodium thiosulfate as a selective inhibitor for non-target microorganisms can be added to enrichment media used to restore injured bacterial cells and Patel and Ray et al teaches that sodium pyruvate and catalase are useful for maximizing repair and colony formation of injured bacterial cells (including Salmonella, S. aureus and Listeria) by acting on the toxic substance hydrogen peroxide and superoxide radicals. Furthermore, it would have been prima facie obvious to additionally add an antibiotic because Strenkoski et al teaches that the pre-enrichment media can comprise a mildly selective inhibitor such as an antibiotic and enrichment media can comprise at least one selective inhibitor or mixtures thereof.

As to the concentrations of sodium pyruvate, sodium thiosulfate and catalase in claims 2 and 22, MPEP 2144.05 states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)." Heck et al teaches concentrations of sodium thiosulfate as a selective inhibitor at a concentration of about 0.03% -0.07% by weight and Patel et al teaches concentrations of catalase and sodium pyruvate that can be use to recover injured bacteria. Thus, it would have been prima facie obvious for one skilled in the art at the time the instant invention was made to arrive workable ranges of catalase and sodium pyruvate and catalase as set forth in claims 2 and 22, with a reasonable expectation of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to recite "catalase at a concentration selected from the group consisting of between 500 and 20,000 IU/L, between 2,000 and 8,000 IU/L and about 5,000 IU/L". Applicants state that support for the amendment is found in claim 2 as filed. This is not persuasive. Original claim 2 as filed stated, catalase at a concentration selected from the group consisting of between 500 and 20,000 μ/L, between 2,000 and 8,000 μ/L and approximately 5,000 μ/L". There is no support in the original claims as filed or in the specification for these concentrations. The original claim 2 contained "μ/L" and not "IU/L". This is new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3, 7, 11-14, 16 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 recites ' "step b comprises in addition to an induction step for at least one surface antigen characteristic of the microorganism sought...". "In addition to an induction step for at least one surface antigen characteristic of the microorganism sought" lacks antecedent basis because claim 1 does not disclose induction step for at least one surface antigen characteristic of the microorganism sought.

Also, the term *about 10g/L* in claim 7 or *about 63 microns* in claim 16 is a relative term which renders the claim indefinite. The term *about* is not defined by the claim, the specification

does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention e.g. the upper or lower limits of 'about 10 g/L".

The term *about 5000 IU/L* in claims 2-3 or *22* is a relative term which renders the claim indefinite. The term *about* is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention e.g. the upper or lower limits of *about 5000 IU/L.*

Claims 11 - "medium" lacks antecedent basis in claim 1.

Claims 11 - discloses at least one substrate comprising one part specific to the enzymatic activity to be indicated and one fluorogenic label, while claim 11 discloses at least one substrate comprising a part specific to the enzymatic activity to be revealed and one label part. Claim 1 discloses a particular type of label i.e. fluorogenic while claim 11 broadly discloses a label. Thus, claim 11 is broadening and does not further limit claim 1.

Claim 14 – discloses that the detection and analysis of fluorescence are carried out by a technique selected from flow cytometry, filtration cytometry and fluorescence microscopy. Claim 1 discloses these techniques already and "detection and analysis of fluorescence" lacks antecedent basis because claim 1 teaches "detecting and counting the fluorescence labeled microorganisms".

Status of Claims

Claims 1-17 and 21-22 are rejected. Claims 18-20 are withdrawn. No claims allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645
/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645